COMPARISON OF TWO METHODS OF PHENYLEPHRINE ADMINISTRATION FOR THE PREVENTION AND TREATMENT OF HYPOTENSION IN CESAREAN SECTION DURING SPINAL ANAESTHESIA

A STUDY OF 100 CASES

DISSERTATION SUBMITTED FOR THE DEGREE OF

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BONAFIDE CERTIFICATE

This is to certify that this dissertation entitled **"COMPARISON OF TWO METHODS OF PHENYLEPHRINE ADMINISTRATION FOR THE PREVENTION AND TREATMENT OF HYPOTENSION IN CESAREAN SECTION DURING SPINAL ANAESTHESIA "** is a bonafide record work done by **Dr. J.VIJAYAKUMAR** under my direct supervision and guidance, submitted to the Tamil Nadu Dr. M.G.R. Medical University in partial fulfillment of University regulation for MD, Branch X –Anaesthesiology.

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DECLARATION

I **DR.J.VIJAYAKUMAR** solemnly declare that this dissertation titled **"COMPARISON OF TWO METHODS OF PHENYLEPHRINE ADMINISTRATION FOR THE PREVENTION AND TREATMENT OF HYPOTENSION IN CESAREAN SECTION DURING SPINAL ANAESTHESIA "** has been done by me. I also declare that this bonafide work or a part of this work was not submitted by me or any others for any award, degree, diploma to any other University or board either in India or abroad.

This is submitted to The Tamilnadu Dr. M. G. R. Medical University, Chennai in partial fulfillment of the rules and regulation for the award of Doctor of Medicine degree Branch–X (Anaesthesiology) to be held in March 2010.

Place: Madurai Dr.J.VIJAYAKUMAR

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INTRODUCTION

Obstetric anaesthesia has become one of the most important subspeciality which compose the widely ranging disciplines of anaesthesia.

Since the days of Sir James Young Simpson and John snow, pioneers of obstetric analgesia and anaesthesia, modern obstetric anaesthesia has become a very safe and scientific speciality.

Universally, there is an increase in the incidence of cesarean sections due to multi-factorial reasons. One of the main reason is the safety of anaesthetics for cesarean section.

Spinal anaesthesia has a time honored place among the options of anaesthesia for cesarean section. The out standing advantages are

1. Relative ease of administration of a spinal anaesthetic.
2. Rapidity of onset
3. Elimination of problems of gastric aspiration and difficult tracheal intubation during general anaesthesia.

0.5 % Bupivacaine hyperbaric is the commonest intrathecal local anaesthetic used in our part of the country for cesarean section.

Conduction anaesthesia however poses its own problems of hypotension and inadequate analgesia. For adequate analgesia, a high block to at least, T4 is necessary and concomitant vasodilatation predisposes to hypotension, even when great care is taken to avoid aortocaval compression.

A widely used method of prophylaxis against hypotension developing during conduction anaesthesia for cesarean section has been

1. Use of left uterine displacement
2. Fluid loading with crystalloids

Spinal anesthesia for cesarean delivery may be associated with hypotension and fetal acidosis (Robert et al, Mueller et al). Many different strategies have been investigated for the prevention of hypotension (usually defined as a decrease in systolic blood pressure [SBP] by more than 20%–30% or to < 90–100 mm Hg), but few have proven to be consistently reliable. Previously, studies have described the use of IV infusions of α agonists to maintain maternal SBP (Ngan et al). In those studies, however, the infusion was started after maternal SBP started to decrease, and in some cases there were marked initial periods of hypotension (Ngan et al). One recent clinical study (Warwick D. Ngan et al) suggested that starting a prophylactic vasopressor infusion immediately after the induction of anesthesia was more effective for reducing both the incidence and frequency of hypotension. However, one concern of this technique is that relatively large doses of vasopressor is likely to be used. Although large doses of drugs such as Phenylephrine and metaraminol are likely to be very effective in maintaining maternal SBP, they may potentially cause detrimental effects on fetal acid-base status because of adverse effects on uteroplacental blood flow.

In this study, prophylactic infusion of Phenylephrine 100 µg/min started immediately after the induction of spinal anesthesia is investigated. A control group received Phenylephrine given by a more conventional method in which 100-µg IV boluses were given as treatment for episodes of hypotension. The hypothesis that, there would be no detrimental effect on fetal acid-base status despite the likelihood that large dose of Phenylephrine would be given when administered by infusion (Ngan et al) is also investigated. The main outcome measurement was umbilical cord arterial (UA) blood pH, which is the most often measured variable as an index of fetal acid-base status (thorp et al).

AIM OF THE STUDY

This study was undertaken with the aim of prospectively comparing two methods of administration of Phenylephrine, Infusion vs Bolus dose in prevention and treatment of hypotension in cesarean section under spinal anaesthesia, and to assess the

1. Incidence and magnitude of hypotension
2. Incidence of adverse effects
3. Fetal outcome
4. Total dose of Phenylephrine used

HISTORY

'THE HISTORY OF CESAREAN SECTION' published by J.H.Young in 1944 indicates that cesarean section was practiced upon dead pregnant woman. The ancient Roman law, known as 'Lex Regia' was practiced by second Roman king during 762-715 B.C by which it was forbidden to bury the dead body of pregnant women without taking out the child. Later during the time of Ceaser, the law became 'Lex Caesarea' and this is the most probable derivation of its present name. The term 'Cesarean section' was used by James Gullimeau in his book of midwifery, published in 1598.

German obstetrician Sager revolutionized the safe technique of cesarean section by introducing his method of suturing the uterus, there by reducing the mortality rate considerably.

Sir James Young Simpson used Diethyl ether for obstetric analgesia on January 1847 and chloroform on 8th November 1847.

When John Snow gave chloroform to Queen Victoria during the birth of her eighth child, Prince Leopold on 7th April 1853, obstetric anaesthesia was rightfully acknowledged by the medical world.

Soon after Bier gave the first intradural spinal block in 1898 it was used in obstetric anaesthesia by Kreis, Doloris, and Malartic between

1900-1902. In 1928 Pitkin published his paper on controlled spinal anaesthesia in obstetrics.

Lignocaine was synthesized by Nils Lofgren and Lundquist in 1943 in Sweden and first used by Gorth in 1948.

Bupivacaine was synthesized in Sweden by Ekenstam and his colleagues in 1957 and used clinically by L.J.Telivuo in 1963.

Phenylephrine was first described in 1910 by Barger and Dale.

ANATOMY OF SUBARACHNOID SPACE

Vertebral canal extends from foramen magnum to the sacral hiatus. It protects the spinal cord.

There are seven cervical, twelve thoracic and five lumbar vertebrae. The sacrum comprises five, and the coccyx four, fused segments. The adult spine presents four curvatures: those of the cervical and lumbar zones are convex forwards (lordosis), those of the thoracic and sacral regions are concave (kyphosis). The former are postural, the latter are produced by the actual configuration of the bones themselves. In the fetus, there is only a single concave-forward curvature; the cervical compensatory curve develops when the newborn infant holds up its head and the lumbar curve follows still later, when the child sits and then stands.

Although the individual vertebra have their own features, they are constructed on a basic pattern as represented by the mid-thoracic vertebra the body, through which the weight of the subject is transmitted, and the vertebral (or neural) arch, which surrounds and protects the spinal cord lying in the vertebral foramen. The arch comprises a pedicle and a lamina on each side, and a dorsal spine. Each lamina, in turn, carries a transverse process and superior and inferior articular processes that bear the articular facets. The pedicles are notched; the notches of each adjacent pair together form an intervertebral foramen through which emerges a spinal nerve. The vertebral column is bound together by several ligaments. They are,

1. Supraspinal ligament – passes longitudinally over the tips of the spinous processes from C7 to the sacrum.
2. Interspinous ligament – connects the adjoining spinous processes together.
3. Ligamentum Flavum – Known as yellow ligament, connects the adjacent laminae composed of yellow elastic fibers. They become progressively thicker from above downwards.
4. Posterior longitudinal ligament – It is on the posterior surface of bodies of vertebra.
5. Anterior longitudinal ligament – It runs along the front of the vertebral bodies.

   There are seven projections from these vertebras.

They are,

a) Three muscular processes – (2-Transverse processes, 1-spinous process for the attachment of muscle and ligaments).
b) Four articular processes – Two upper & two lower which in the lumbar region prevent rotation but allow limited flexion and extension between contiguous vertebrae.

Vertebral canal formed by these structures has deficiencies posteriorly in the midline called inter laminar foramina which enlarge in flexion accessible for the passage of spinal needle. The direction of spinous process determines the direction of spinal needle.

SPINAL CORD:

It is the direct continuation of the medulla oblongata extending from the upper border of the atlas to the first lumbar vertebra, below which there is leash of nerve roots termed cauda equina. Spinal nerves are 31 pairs totally. They are 8 Cervical, 12 Thoracic, 5 Lumbar, 5 Sacral, and 1 Coccygeal.

Each of the spinal nerve is composed of anterior and posterior roots uniting at the intervertebral foramina and forms a nerve trunk. Membranes covering the spinal cord from outside are dura mater, arachnoid mater and piamater. Dura and arachnoid mater end at S_2 level. Piamater is closely applied to the spinal cord.

BLOOD SUPPLY:

It is from the anterior spinal artery which is a branch of vertebral artery and also by a pair of posterior spinal arteries which arise from the posterior inferior cerebellar arteries. There is no anastamosis between these arteries.

SPINAL VEINS:

The spinal veins are arranged into anterior and posterior plexus which are draining into vertebral, azygos and lumbar veins.

CEREBROSPINAL FLUID:

This is an ultra filtrate of the blood plasma from choroid plexus of the lateral ventricles with a pH of 7.32 (7.27-7.37)

It is a clear, colourless fluid found in the cranial and spinal subarachnoid spaces and in the ventricles of the brain.

The total volume of CSF in an average adult ranges from 120-150ml of which 25-35ml is in the spinal subarachnoid space.

Composition of cerebrospinal fluid:

Specific gravity	-	1.006 (1.003-1.009) at 37^0C
Pressure	-	60-80mm of water
PCO_2	-	48mmHg
$HCO3^-$	-	23meq/l
Na^+	-	133-145meq/l
Cl^-	-	15-20mg/dl
Sugar	-	45-80mg/dl
Ca^+	-	2-3meq/l
$PO4^-$	-	1.6mg/dl

Mg^{+}	-	2-2.5mg/dl
Lymphocytes	-	0-5cells/cu mm
Protein	-	23-38mg/dl

An important factor that determines the spread of drug in cerebrospinal fluid is the density of the drug in relation to that of cerebrospinal fluid (Baricity) which is 1.003-1.009. Hyper baric solution is one which is denser than CSF at $37^{0}C$.

PHYSIOLOGY OF SUBARACHNOID BLOCK

Subarachnoid block implies the temporary interruption of nerve transmission within the subarachnoid space by injections of local anaethetics. The blockade of nerve fibres occur in the order of temperature, pain, proprioceptive and then motor fibres.

FACTORS INFLUENCING BLOCK HEIGHT:

a - Site of injection

b - Angulation of needle

c - Characteristic of local anaesthetic

d - Dose of local anaesthetic

e - Position of the patient during and after injection

f - Anatomic configuration of spinal column.

g - Patient height (at extremes)

h - Volume of cerebrospinal fluid

i - Reduced cerebrospinal fluid with increased intra abdominal pressure (eg. Pregnancy)

a) Effects on Cardio Vascular System:

Most important physiological responses to subarachnoid block involve cardio vascular system which is due to autonomic denervation.

Local anaesthetics and vasoactive substances administered in small doses intrathecally leads to direct cardiovascular effect.

Level of sympathetic denervation determines the magnitude of cardio vascular system responses, but the relationship is neither predictable nor precise.

Sympathetic denervation produces arterial and more physiologically important arteriolar dilatation and vasodilatation in the venous circulation produces fall in blood pressure.

Due to Bainbridge reflex, the fall in blood pressure is associated with bradycardia; blockade of cardiac sympathetic fibre from T1-T4 is an additional factor that causes bradycardia.

b) Effects on Respiratory System:

Respiration is not depressed normally. High spinal can cause paralysis of intercostal muscles but resting tidal volume, maximum inspiratory volume, respiratory rate, ABG, negative intrapleural pressure and also the phrenic nerve are unaffected. Hypoxia may accompany hypotension and is corrected by oxygen administration via face mask.

c) Gastro Intestinal Effect:

Preganglionic fibres from T_5-L_1 are inhibitory to gut. So in sympathetic blockade the small intestine contracts with relaxed sphincters and peristalsis remains normal. Handling of viscera causes discomfort and bradycardia since vagus is not blocked.

d) Hepatic and Renal Effects:

The hepatic blood flow decreases and is directly proportional to the decrease in blood pressure. There may be normal hepatic oxygen extraction. Renal blood flow is maintained by auto regulation and does not decrease till mean arterial pressure goes below 50mmHg.

e) Genito Urinary System:

Sphincters of bladder are not relaxed, and tone of the ureter is not greatly altered. Urinary retention occurs. Penis is often engorged. Uterine tone is unchanged in pregnancy. In the absence of hypotension spinal anaesthesia has got no effect on the progress of labour and uterine blood flow.

f) Metabolic and hormonal effect:

Spinal anaesthesia blocks hormonal and metabolic responses to nociceptive stimuli arising from the operative site. It minimizes the rise in blood sugar, coritsol, catecholamine, renin and aldosterone release associated with stress. Post operative negative nitrogen balance and secretion of antidiuretic hormone are inhibited.

g) Thermo Regulation:

Hypothermia results from heat loss to the cold environment due to vasodilatation.

ANATOMICAL AND PHYSIOLOGICAL ANAESTHETIC IMPLICATIONS IN PREGNANT PATIENTS

Maternal changes in pregnancy occur as a result of:

Hormonal alterations

Mechanical effects of the gravid uterus

Increased metabolic and O2 requirements

Metabolic demands of the fetoplacental unit

Hemodynamic alterations associated with the placental circulation.

CARDIOVASCULAR SYSTEM:

Stimulus behind Cardiovascular changes is mainly endocrine

CARDIAC OUTPUT:

Increases from 5^{th} week, and the maximal levels are reached at 32 weeks.50% of the increase in cardiac output occurs at 8^{th} week.

Cardiac output is the product of heart rate and stroke volume.

Heart rate increases by 20- 30 % and stroke volume increases by 20- 50 %

BLOOD PRESSURE:

Gradual fall in blood pressure occurs, systolic blood pressure decreases by 5-10 mmHg and diastolic blood pressure decreases by10-15mmHg, so there is an increase in pulse pressure.

VASCULAR RESISTANCE:

There is a decrease in systemic vascular resistance by 20% and a decrease in pulmonary vascular resistance by 30 %. Decrease in systemic vascular resistance causes a low resistance utero placental circulation. Blood flow to organs is not uniform, uterus receives 700-800 ml/min which is10 % of cardiac output, and blood supply to breast doubles which is 2% of cardiac output.

AORTOCAVAL COMPRESSION:

After 20 weeks of pregnancy, the enlarged uterus compresses the IVC in supine position so there is a decrease in venous return to the heart.

SUPINE HYPOTENSION SYNDROME:

Characterized by hypotension, nausea, vomiting, sweating & pallor. Gravid uterus also compresses the aorta in supine position so decrease in blood flow to lower extremities and uteroplacental circulation. Aortocaval compression is an important preventable cause of fetal distress. Anaesthetics and drugs that cause vasodilatation or techniques that cause sympathectomy increase the aortocaval compression. Parturients with 20 weeks or longer gestation should not be placed supine without left uterine displacement, accomplished by placing a wedge (>15°, CARDIFF'S WEDGE) under the right hip.

Parameter	Change	Amount (%)
Heart rate	Increased	20–30
Stroke volume	Increased	20–50
Cardiac output	Increased	30–50
Contractility	Variable	±10
CVP	Unchanged	-
PCWP	Unchanged	-
SVR	Decreased	20
SBP	Slight decrease	Mid trimester ,10–15
PVR	Decreased	30
PAP	Slight decrease	-

LABOUR:

Cardiac output increases further in labour, basal cardiac output in between uterine contractions increases by 13% in Ist stage of labour. Late in Ist stage of labour cardiac output increases by 34% with each contraction.

PUERPERIUM:

Cardiac output remains elevated for the Ist 24 hrs after delivery, and then falls progressively. Cardiac output decreases by 28% by 2 weeks after delivery, with 20% reduction in heart rate and 18% decrease in stroke volume.

ECG:

ECG shows left axis deviation, right bundle branch block, ST segment depression of 1 mm on left precordial leads, Q waves in lead III ,T-wave inversion in leads III, V2 , and V3

CHEST RADIOGRAPHY:

Apparent cardiomegaly, Enlarged left atrium (lateral views), Increased vascular markings, straightening of left-sided heart border, postpartum pleural effusion

HAEMATOLOGY:

BLOOD VOLUME:

An earliest and most fundamental change in pregnancy is increase in blood volume which is detectable at 6th week, which is greatest during the II trimester and reaches a plateau at 34- 36 weeks. At term, blood volume increases by 48% more than non pregnant values. Trigger for increase in blood volume is hormonal. By term, plasma volume increases by upto 45%, whereas red cell volume increases by 30%. This differential increase is the cause for physiological anemia of pregnancy. The point of greatest difference being 28-30 weeks of gestation. Increase in blood volume compensates for blood loss at delivery, which is 500 ml for vaginal delivery and 800 – 1000 ml for Cesarean section.

COAGULATION

Pregnancy is a state of hypercoagulability and platelet turnover. Increased levels of most coagulation factors, Fibrinogen & Factor VII are markedly increased. Platelet count is slightly decreased in pregnancy.

PLASMA PROTEINS:

Total plasma protein concentration decreases from 70- 60 gm/litre, due to decrease in plasma albumin concentration. The overall effect is decrease in colloid osmotic pressure and increased risk of oedema.

PUERPERIUM:

Immediately after delivery, if blood loss is not excessive the blood volume increases. At the end of puerperium the blood volume decreases to 10% above pre pregnant levels. Plasma albumin and colloid osmotic pressure becomes normal with in 6 weeks of delivery.

RESPIRATORY SYSTEM

Marked changes in respiratory system occur in tandem with changes in cardiovascular system which causes increased O2 uptake and CO2 elimination.

ANATOMY:

Generalized vasodilatation of skin and mucous membrane due to progesterone mediated relaxation of vascular smooth muscle occurs. Capillary engorgement of nose, oropharynx and larynx occurs, and voice change and difficulty with nasal breathing also occurs.

ANTICIPATED DIFFICULT INTUBATION

There is predisposition of upper airways to trauma, bleeding and obstruction, so gentle laryngoscopy and use of small ETT is advised (6.0-7.0). Diaphragm is elevated 4 cm by uterine enlargement. Increase in chest wall circumference by 5-7 cm. Subcostal angle increases from 68° to 103°. Diaphragmatic movements are not hindered. Abdominal muscles are less active

LUNG VOLUMES

Tidal volume increases with gestation, and by term the increase is 40% more than non pregnant women. Vital capacity remains unchanged, respiratory rate increases by 15%, and total lung capacity is slightly decreased. Minute volume increases by 40%, and changes are detectable by 6^{th} week and these changes are due to progesterone. There is increased alveolar ventilation; VD/VT remains unchanged, increased physiological dead space. Functional residual capacity (FRC) decreases, this decrease starts from II trimester, and at term it decreases by 20%. Closing capacity (CC) remains unchanged. O2 consumption increases by 20- 50% due to increased demands. Respiratory quotient increases from a pre pregnant value of 0.76 to 0.83 in late pregnancy .Combination of decreased FRC, increased VO2, decreased FRC/CC ratio causes a rapid O2 desaturation during periods of apnea.

CENTRAL NERVOUS SYSTEM:

There is increased sensitivity to both general and regional anaesthetics. Minimum alveolar concentration is progressively decreased during pregnancy by 40%.

Causes:

1. Maternal hormone like progesterone
2. Endogenous opioid
3. Surge in β endorphin levels during labour and delivery

Enhanced sensitivity to local anaesthetics during regional anaesthesia, so the dose is reduced by 30% .Neural blockade occurs at lower concentration of local anaesthetics.

RENAL SYSTEM:

Renal blood flow increases by 80% in early pregnancy and falls to 60% in III trimester due to relative hypervolemia of pregnancy and increased secretion of hormones. GFR increases by 50% due to dilutional effect of plasma volume expansion so decreased plasma creatinine and urea. “Hence normal renal indices in pregnancy are lower than in the non pregnant state.”

GASTROINTESTINAL SYSTEM

Generalized relaxation and decreased motility of gastro intestinal tract. Hypersecretion of gastric acid occurs and gastric emptying is delayed. With a gastric pH of less than 2.5 and gastric volume of more than 25 ml, there is an increased risk of aspiration pneumonitis.

“SO ALL PARTURIENTS ARE CONSIDERED TO BE HAVING FULL STOMACH. THEREFORE RAPID SEQUENCE INTUBATION AND SELLICK’S MANEUVER SHOULD BE APPLIED”.

Opioids and anticholinergics decrease lower esophageal sphincter pressure which facilitates gastro esophageal reflex and delays gastric emptying.

METABOLIC EFFECTS:

Pregnancy is an accelerated state of starvation, so there is decreased blood glucose and amino acid levels, increased free fatty acids, triglycerides and ketones. Pregnancy is a diabetogenic state so increased insulin secretion occurs. Glucose crosses placental barrier by facilitated diffusion. Thyroid enlargement is by relative hyper stimulation of the gland by human chorionic gonadotropin and increased thyroid binding globulin. Increased Total T4 and T3. Free T4, T3 and TSH remains normal, serum calcium is decreased and ionized calcium is normal.

PHARMACOLOGY OF DRUGS

a) Bupivacaine:

Bupivacaine is an amide linked local anaesthetic. It is a hydrochloride salt of 1-butyl-N-(2, 6- dimethylphenyl) piperidine-2-carboxamide and is presented as a racemic mixture.

- It was synthesized by Ekenstam and Egner
- First reports of its use were published in 1963 by Telivuo.
- It is derived from Mepivacaine and is very stable compound and may be autoclaved repeatedly.

Pka is	-	8.1
Molecular weight	-	288
Protein binding	-	95%
Lipid solubility	-	28
Elimination half life	-	210mts
Toxic plasma concentration	-	>1.5µg/ml
Approximate duration of action	-	175mts

Availability:

Ampoules	-	0.5% Bupivacaine hydrochloride with dextrose (Heavy) 4cc
	-	0.5% Bupivacaine hydrochloride 4cc (plain)
Vials	-	0.25% and 0.5% Bupivacaine hydrochloride 20cc
Dosage	-	Maximum dosage 3mg/kg body weight.

Uses:

- Spinal anaesthesia
- Epidural anaesthesia
- Caudal anaesthesia
- Continuous epidural anaesthesia
- Peripheral nerve block

Onset time and duration of action

Site of action	Onset (minutes)	Duration (minutes)
Intrathecal	5	90-120
Epidural	15-20	165-225
Brachial plexus	15-20	600

Pharmacokinetics:

Once injected intrathecaly, it gets absorbed by the nerve rootlets and results in the desired effect. It is rapidly absorbed from the site of injection, but the rate of absorption depends on the vascularity at the site and presence of vasoconstrictors.

High lipid solubility of bupivacaine makes it easy for nerve and vascular tissue penetration.

80-95% of the absorbed bupivacaine binds to the plasma proteins.

Distribution:

Rapid distribution phase: (α)

In this phase the drug is distributed to highly vascular region. $t1/_2$ of α - being 2.7 minutes.

Slow disappearance phase: (β)

In this phase the drug distributes to slowly equilibrating tissues. $t1/_2$ of β – being 28mts.

Biotransformation and excretion phase: (δ)

$T1/_2$ of δ is 3.5hours clearance is 0.47 litre/minute.

Biotransformation:

Possible pathways of metabolism of bupivacaine include aromatic hydroxylation and conjugation. Only the N-dealkylated metabolite, N-desbutyl bupivacaine has been measured in blood (or) urine after epidural (or) spinal anaesthesia. Alpha1 acid glycoprotein is the most important plasma protein binding site of bupivacaine and its concentration is increased by many clinical situations including post operative trauma.

Excretion:

It is through the kidney; 4-10% of the drug is excreted unchanged.

Mode of Action:

a) Site of action:

i) The spinal nerve rootlets, fine nerve filaments having a large surface area are exposed to the local anaesthetics.

ii) Posterior and lateral aspects of the spinal cord itself.

b) Sodium Channel blockade:

They impede sodium ion access to the axon interior by occluding the transmembrane sodium channels thus delaying the process of depolarization and axon remains polarized. It is a non-depolarization blockade.

Pharmacodynamics:

It has got a longer duration of action but a slower onset.

Cardio vascular system:

It reduces cardiac output by reducing the sympathetic tone, by slowing the heart rate and by reducing the venous return, it produces a fall in arterial blood pressure but it is relatively slow and is seldom very profound.

It produces a fall in central venous pressure. It causes an increase in lower limb blood flow. It causes a reduction in incidence of deep vein thrombosis.

Respiratory System:

Spinal blockade seldom, if ever causes respiratory problem.

Gastro intestinal tract:

There is an increase in gastro intestinal motility and emptying of the gastric contents is better.

Toxicity:

Toxicity is related to plasma level of unbound drug and more likely due to an inadvertent intravenous injection. Systemic toxicity reactions primarily involve central nervous system and cardio vascular system. The blood level required to produce central nervous system toxicity is less than that required to produce circulatory collapse.

Central Nervous System Toxicity:

Initial symptom includes feeling of light headedness and dizziness, followed by visual and auditory disturbances. Objective signs are excitatory and include shivering, muscle twitching and tremor. Ultimately generalized tonic, clonic seizures occurs.

Cardiovascular System Toxicity:

The rate of depolarization in fast conducting tissue of purkinje fibres and ventricular muscle is decreased. The rate of recovery of bupivacaine induced block is slower than that of lignocaine. Extremely high concentration of the drug causes sinus bradycardia and cardiac arrest.

b) Pharmacology of Phenylephrine:

- It was first described in 1910 by Barger and Dale
- Synthetic noncatecholamine
- Also called as neosynephrine
- Stimulates α1 adrenergic receptors by a direct effect
- Small part of pharmacologic response being due to its ability to evoke the release of norepinephrine (indirectly acting)

Dose of Phenylephrine necessary to stimulate α1 receptor is far less than the dose that stimulates α2 receptor, so venoconstriction is greater than arterial constriction

STRUCTURALLY:

It differs from epinephrine in lacking a 4-hydroxylgroup on benzene ring

Clinically Phenylephrine mimics the effects of norepinephrine but is less potent and longer lasting

PHARMACOKINETICS:

Response to subcutaneous dose takes 10 minutes

Response to intramuscular dose takes 15 minutes

Duration of action to subcutaneous dose is 1 hour

Duration of action to intramuscular dose is 2 hours

I.V injection is effective for upto 20 minutes

Metabolized in liver by Mono amine Oxidase (MAO) an enzyme which is present in the gastrointestinal tract and the liver

AVAILABILITY:

Ampoule - each ml contains 10 mg Phenylephrine hydrochloride
Available as 1 ml

Vials - available as 5 ml vial

CONTRAINDICATIONS:

Hypersensitivity to Phenylephrine or any component of the formulation causes hypertension and ventricular tachycardia.

Oral : not to be used within 14 days of MAO inhibitor therapy

Ophthalmic : avoided in narrow-angle glaucoma

CLINICAL USES:

Phenylephrine, 50 to 200 µg IV to treat blood pressure decreases that accompany sympathetic nervous system blockade by regional anaesthetic or peripheral vasodilatation which accompanies administration of injected or inhaled anaesthetic.

Useful in patients with CAD and in patients with aortic stenosis because this drug in contrast to other sympathomimetics increases the coronary perfusion pressure without chronotropic side effects.

Topically administered Phenylephrine is a nasal decongesant and produces mydriasis without cycloplegia.

Phenylephrine like epinephrine is effective in prolonging spinal anaesthesia when added to local anaesthetic solution that is placed in the subarachnoid space. Phenylephrine prolongs spinal anesthesia with tetracaine, Tetracaine + Phenylephrine the duration is 406 ± 63mins (5 mg) compared to tetracaine alone 273 ± 90 mins. Phenylephrine has been used in epidural anesthesia less widely than in spinal anesthesia, perhaps because it does not reduce peak blood levels of local anesthetic as effectively as epinephrine does during epidural use.

In obstetric anaesthesia Phenylephrine is associated with a higher umbilical artery pH at delivery than ephedrine.

EYE:

Phenylephrine is an α-adrenergic agonist applied topically to dilate the pupil.

Systemic absorption of the 10% solution is associated with severe hypertensive reactions. The 2.5% concentration is safer, but may exacerbate hypertension in some patients.

Narrow angle glaucoma is a contraindication to Phenylephrine use.

NASAL DECONGESANT:

Topical vasoconstrictor alone or in combination with lidocaine. Guidelines on the topical use of Phenylephrine in the operating room recommend the following:

1. Initial phenylephrine dose should not exceed 0.5 mg, and in children weighing 25 kg or less, it should not exceed 20 µg/kg.
2. Blood pressure and pulse should be closely monitored.
3. The dose should be administered in a calibrated syringe and should be verified by a physician.
4. The anesthesiologist should be aware of all medications given.
5. Severe hypertension should be treated immediately with direct vasodilators or α-receptor antagonists.
6. β-Receptor blockers and calcium channel blockers should be

avoided. They can worsen cardiac output and result in pulmonary edema.

7. If a β-receptor blocker is used to treat hypertension, glucagon administration should be considered to counteract the loss of cardiac contractility.

SIDE EFFECTS:

Cardiovascular system:

Rapid I.V injection of Phenylephrine to patients with coronary artery disease produces dose dependent peripheral vasoconstriction and increase in systemic blood pressure that are accompanied by decrease in cardiac output. In spite of reduction in cardiac output there is an increase in coronary blood flow. Decreased cardiac output is due to increased afterload (constriction), and reflex mediated bradycardia.

Renal, splanchnic and cutaneous blood flows are decreased. Pulmonary artery pressure is increased

Metabolic effects:

Stimulation of α receptors by a continuous infusion of Phenylephrine during acute potassium loading interferes with the movement of potassium ions across cell membrane into cells.

TREATMENT OF OVER DOSE:

Systemic hypertension induced by topically applied or injected α agonists may not require treatment. The duration of action of Phenylephrine and Epinephrine is brief and hypertension may resolve spontaneously without pharmacologic interventions.

In case of severe hypertension, vasodilating drugs such as nitroprusside or nitroglycerine is recommended.

NEURAXIAL ANAESTHESIA AND FETAL ACIDOSIS

The use of neuraxial anesthesia has dramaticaly increased, and data suggest that the use of general anesthesia for cesarean section has been steadily decreasing. Neuraxial anesthesia techniques have several advantages, including a decreased risk of failed intubation and aspiration of gastric contents, avoidance of depressant agents, and the ability of the mother to remain awake and enjoy the experience of child birth. In addition, it has been suggested that blood loss is reduced under regional anesthesia for cesarean delivery.

Although epidural, spinal, continuous spinal and CSE techniques have all been advocated, most straightforward cesarean sections are now performed with single-shot spinal anesthesia, which has been found to be faster, provide a superior block, and are more cost effective, especially as compared with epidural anesthesia.

SPINAL ANESTHESIA: Spinal (subarachnoid) anesthesia offers many advantages for cesarean delivery. It has a very rapid onset and provides a dense neural block. Because of the small doses used, there is little risk of local anesthetic toxicity and minimal transfer of drug to the fetus. In addition, failures (including incomplete or patchy blocks) are very infrequent with spinal anesthesia. Disadvantages of this technique include the definite duration of anesthesia and a higher incidence of hypotension.

The major adverse fetal effect of regional anaesthesia and its sympathetic blockade is uteroplacental hypoperfusion, which leads to an acute fall in intervillous blood flow with the potential for fetal acidemia. The type of fetal acidemia associated with anaesthesia of any method, including general anaesthesia, is predominantly "Respiratory," suggesting that an acute event is the proximate cause of the fetus's acid-base condition. Specifically, PaCO2 values increased significantly in acidemia fetuses. Metabolic acidemia is rare in the acute causes of hypotension.

SAMPLING PROCEDURE: Umbilical cord blood analysis is assumed to give a picture of the acid–base balance of the infant at the moment of birth when the umbilical circulation is arrested by clamping of the cord. However, from this moment onwards the umbilical cord blood, if it remains in continuity with placenta, will demonstrate progressive change in acid–base status due to ongoing placental metabolism and gas exchange. Small changes in umbilical pH occur within 60 seconds of delivery, and over 60 minutes cord arterial or venous pH can fall by more than 0.2 pH units. Similar changes occur in blood sampled from placental surface vessels except that they are larger and less predictable. These changes are not observed if the cord is doubly clamped at birth, isolating a segment of cord blood from both the placenta and the environment. The umbilical vein is larger and easier to sample from than the umbilical artery, and when only a single sample can be obtained because of sampling difficulties it is likely to be venous. So paired samples are obtained.

WHAT IS A NORMAL CORD pH? : Many authors have studied normal umbilical blood biochemistry and acid–base status. Most available data relate to infants born at full term. Parity, breech presentation, mode of delivery and many other factors influence cord gas values.

	Umbilical artery pH	**PCO2 (kPa)**	**Umbilical vein pH**	**PCO2 (kPa)**
Victory et al 2004	7.24		7.33	
Thorp et al 1989	7.24	6.69	7.32	5.83
Helwig et al 1996	7.26	7.05	7.34	5.45
Dickinson et al 1992	7.26	7.05	7.33	5.77
Riley and Johnson1993	7.27	6.69	7.34	5.41

Umbilical cord blood gas analysis is recommended in all high-risk deliveries and is performed after all deliveries in some centres. For optimal interpretation paired umbilical arterial and venous samples should be taken soon after birth from a segment of cord that has been doubly clamped to isolate it from the placenta. Low cord pH in infants who are vigorous at birth and free of cardiopulmonary compromise does not indicate an increased risk of adverse outcome. Infants with pH ,7.0 at birth who are not vigorous are at high risk of adverse outcome. Identification of infants at risk of encephalopathy is especially important now that early intervention is being considered. Analysis of paired arterial and venous specimens can give insights into the aetiology of the acidosis. In combination with other clinical information, normal paired arterial and venous cord blood gas results can usually provide a robust defense against a suggestion that an infant had an intrapartum hypoxic-ischaemic event.

REVIEW OF LITERATURE

1. Rout CC et al (1992) concluded that Rapid administration of crystalloid preload does not decrease the incidence of hypotension after spinal anaesthesia for elective Caesarean section. They found that pre loading of 1 litre of crystalloid solution infusion during the 10 min preceding the administration of spinal anaesthesia for cesarean section in combination with a prophylactic infusion of ephedrine did not reduce the incidence, severity, duration of hypotension.

2. Thomas et al (1996) did randomized trial of bolus Phenylephrine or ephedrine for maintenance of arterial pressure during spinal anaesthesia for Caesarean section, Thirty-eight healthy women undergoing elective Caesarean section under spinal anaesthesia at term were allocated randomly to receive boluses of either Phenylephrine 100 micrograms or ephedrine 5 mg for maintenance of maternal arterial pressure. Mean umbilical artery pH [95% CI] was higher in the Phenylephrine group (7.29 [7.28-7.30]) than in the ephedrine group (7.27 [7.25-7.28]). The results of the present study support the use of phenylephrine for maintenance of maternal arterial pressure during spinal anaesthesia for elective cesarean section.

3. HALLet al (1994) compared infusions of phenylephrine and ephedrine and infusion of Phenylephrine 10 µg min^{-1} with bolus doses of 20 µg was shown to be significantly more effective in maintaining systolic arterial pressure within 20% limits of baseline compared with an infusion of ephedrine 1 or 2 mg min^{-1} with bolus doses of 6mg .

4. Cooper et al, studied the effect of intravenous vasopressor on spread of spinal anaesthesia and fetal acid–base equilibrium. It was found that rostral spread of spinal hyperbaric bupivacaine to be less with prophylactic phenylephrine than with ephedrine. It was observed that an unexpectedly high incidence of fetal acidosis with ephedrine and found evidence that longer spinal-delivery intervals increase the risk of fetal acidosis developing with ephedrine, but not phenylephrine.

5. Afshari et al (2006) Compared prophylactic infusion of ephedrine and phenylephrine during Cesarean section under spinal anaesthesia. Spinal anaesthesia for caesarean delivery may be associated with hypotension and fetal acidosis. Prophylactic infusion of phenylephrine immediately after the induction of anaesthesia appears to be a more effective approach than administration of ephedrine to reduce the incidence, frequency and severity of hypotension. Furthermore, Phenylephrine appears to be associated with better fetal acid-base status than is ephedrine.

6. Moran et al(1999) studied about Phenylephrine in the prevention of hypotension following spinal anesthesia for cesarean delivery. Here the maternal venous, umbilical artery, and umbilical vein blood gases were measured, and neonatal Apgar scores and early neonatal neurobehavior scale scores were assessed. In the ephedrine group, umbilical artery pH was 7.28 ± 0.01 (mean ± SEM), umbilical artery partial pressure of carbon dioxide (PCO_2) was 56.6 ± 1.4 mmHg, and umbilical artery base deficit was 2.2 ± 0.04 meq. In the phenylephrine group, umbilical artery pH was 7.32 ± 0.01, umbilical artery PCO_2 was 52.1 ± 1.3 mm Hg, and umbilical artery base deficit was 0.38 ± 0.35 meq. There were significant differences between the groups in mean umbilical artery pH, PCO_2 and base deficit, although all values obtained were within normal limits. There were no significant differences between the groups in the remaining acid-base values, neonatal Apgar scores, early neonatal neurobehavior scale scores, or frequency of maternal nausea and vomiting. It was concluded that Phenylephrine is as effective as ephedrine in the treatment of maternal hypotension, and when used in small incremental bolus injections, it appears to have no adverse neonatal effects in healthy, nonlaboring parturients.

7. Mercier et al,(2001) studied about Phenylephrine added to prophylactic ephedrine infusion during spinal anesthesia for elective cesarean section, hypotension occurred less frequently in the ephedrine-phenylephrine group than in the ephedrine alone group: 37%versus 75% ($P = 0.02$). Ephedrine (36 ±16 mg, mean ± SD) plus 178 ±81 μg phenylephrine was infused in former group, whereas 54 ±18 mg ephedrine was infused in the latter. Median supplemental ephedrine requirements and nausea scores (0-3) were less in the ephedrine-phenylephrine group (0 vs. 12 mg, $P = 0.02$; and 0 vs. 1.5, $P = 0.01$, respectively). Umbilical artery p H values were significantly higher in the ephedrine-phenylephrine group than in the group that received ephedrine alone (7.24 vs. 7.19). Apgar scores were similarly good in both groups. They concluded that Phenylephrine added to an infusion of ephedrine halved the incidence of hypotension and increased umbilical cord p H.

8. ***Schwinn et al (1989) studied the*** time course and hemodynamic effects of alpha-1-adrenergic bolus administration in anesthetized patients with myocardial disease. Phenylephrine is frequently administered as an intravenous bolus to increase blood pressure, yet the acute time course and hemodynamic effects of bolus Phenylephrine in patients with myocardial disease have not been reported. Therefore 50 randomized intravenous bolus doses of Phenylephrine (50, 100, 150, or 200 μg) were given to 18 patients during anesthesia for elective coronary artery surgery. Esophageal doppler techniques were used to continuously monitor cardiac output (CO); mean arterial pressure (MAP), CO, and calculated systemic vascular resistance (SVR) were recorded every 5 seconds for a total of 2 minutes. CO (–.58 ± 11, –.68 ± .13, –.73 ± 20, –.77 ± 18 $Lmin^{-1}$). Hypertension, increased age, low preoperative ejection fraction, high baseline CO, and low baseline SVR significantly ($P < 0.05$) decreased hemodynamic responses to Phenylephrine .In conclusion, bolus IV Phenylephrine in patients with myocardial disease increases MAP and SVR and simultaneously decreases CO; these peak hemodynamic events occur approximately 42 seconds after Phenylephrine administration.

9. *Stephen et al (2001) studied* the effects of an increase of central blood volume before spinal anesthesia for cesarean delivery: A qualitative systematic review, he performed a systematic review to determine whether fluid loading reduced the incidence of low blood pressure after spinal anesthesia for cesarean delivery. It was concluded in the study that no technique totally eliminates the occurrence of hypotension, colloid administration (starch or gelatin containing fluids) and leg wrapping were the most effective.

10. Brooker et al (1997) studied about the treatment of hypotension after hyperbaric tetracaine spinal anesthesia: A randomized, double-blind, cross-over comparison of Phenylephrine and Epinephrine, and concluded that Epinephrine management of tetracaine induced spinal hypotension increases heart rate and cardiac output and restores systolic arterial pressure but does not restore mean and diastolic blood pressure. Phenylephrine management of tetracaine spinal-induced hypotension decreases heart rate and cardiac output while restoring systolic, mean, and diastolic blood pressure.

MATERIALS AND METHODS

After getting the approval from the ethical committee, the study was conducted in 100 patients, who all were primi gravidas undergoing emergency cesarean section. After getting consent and explaining the procedure details, the anaesthetic technique was performed.

SELECTION OF PATIENTS:

The patients selected for this study were of ASA Risk I. It was a randomized double blinded study. The usual indications for the cesarean section were cephalopelvic disproportion, breech presentation, and premature rupture of membranes. Patients exhibiting the following were excluded from the study.

- Diabetes mellitus
- Pregnancy induced hypertension
- Obesity
- Multiple pregnancy
- Cardiac disease
- Coagulopathy
- Renal impairment

Age group:

Age of the patients ranged from 18 to 30 yrs

METHOD OF STUDY:

The following anaesthetic equipments and drugs were kept ready before the performance of subarachnoid block.

- Boyles machine with oxygen cylinder
- Laryngoscope with blades of various sizes
- Airway and endotracheal tubes in all sizes
- Suction apparatus
- Emergency drugs like ephedrine, dopamine, atropine and adrenaline

PROCEDURE DETAILS:

The preoperative baseline parameters like pulse rate, blood pressure, respiratory rate were recorded. Three readings were taken and the average of the three was taken as the mean baseline value of the patient.

IV line started with 18 gauge intravenous cannula and the patient was infused with Ringer lactate solution at the rate of 5 ml per minute. They are premedicated with Inj. Ranitidine 50 mg and Inj.Metoclopramide 10 mg intravenously.

The subarachnoid block was performed under strict aseptic precaution with the patient in right lateral position with a 25 gauge Quincke spinal needle in the L2-L3 interspace, and 1.8 ml of 0.5% hyperbaric Bupivacaine was injected after ensuring free flow of cerebrospinal fluid.

The patients were immediately turned to the supine position with a wedge of 10 cm below the right buttock.

The patients were randomly allocated to receive the study drugs, either Phenylephrine infusion or bolus dose. In the infusion group, Phenylephrine 100µg /min was infused for the initial 3 minutes after the subarachnoid block and were supplemented with 100µg infusion, whenever the systolic blood pressure was below the baseline value.

In the control group Phenylephrine 100µg bolus was given when the systolic blood pressure decreased to 20% of the baseline value.

The following were noted and recorded.

1. Pulse rate and blood pressure every one minute until delivery of the baby and every five minutes thereafter.
2. The time interval between subarachnoid block to skin incision, skin incision to uterine incision, and uterine incision to delivery of baby.

3. APGAR scores at 1 minute and 5 minutes to asses neonatal outcome.
4. Total dose of the Phenylephrine used until the delivery of the baby in both groups.
5. Total episodes of the hypotension.
6. Upper level of sensory anaesthesia after 10 minutes.
7. Incidence of nausea and vomiting.
8. Supplemental oxygen requirement.
9. Total duration of surgery.

After delivery of the baby, blood pressure and heart rate were maintained by infusing fluids and vasopressors and the umbilical cord was clamped at two ends, blood samples were taken from umbilical artery and umbilical vein for blood gas analysis.

Bradycardia was treated with injection atropine 0.3 mg IV, if the heart rate was below 50 per minute and oxygen was supplemented if the oxygen saturation dropped below 95%.

POST OPERATIVE OBSERVATION:

Immediately after the surgery, Pulse rate and blood pressure were recorded. Patients were transferred to recovery room and observed till the time of total regression of analgesia and recovery from motor paralysis.

Blood pressure and pulse rate were recorded at regular intervals of 30 mins.

Once the patient is recovered and the vital functions are stable, patients were transferred to post-operative ward. In the post-operative ward the vital parameters were monitored. Patients were followed up till discharge.

Statistical Tools

The information collected regarding all the selected cases were recorded in a Master Chart. Data analysis was done with the help of computer using Epidemiological Information Package (EPI 2002) developed by Centers for Disease Control and Prevention (CDC), Atlanta for W.H.O.

Using this software, frequencies, percentage, range, mean, standard deviation, x^2 and 'p' values were calculated. A 'p' value less than 0.05 is taken to denote significant relationship

OBSERVATION AND RESULTS

Table 1: Age distribution

Age group	INF Group		CON Group	
	No.	%	No.	%
Upto 20	2	4	-	-
21-25	33	66	40	80
26-30	14	28	10	20
>30	1	2	-	-
Total	50	100	50	100
Range	20-32		21-27	
Mean	24.2		24.1	
S.D.	2.9		1.7	
‘p’	0.5844 Not significant			

The demographic data of the patients included in this study showed no significant difference between both groups**.**

Table 2 : Pre operative parameters

Variables (preoperative)	INF group		CON group		'p'
	Mean	SD	Mean	SD	
Systolic BP	121.6	9.6	122.4	8.6	0.5163 not significant
Diastolic BP	77.7	5.8	76.8	4.3	0.5012 not significant
Pulse rate	82.2	5.9	80	8.6	0.5101 not significant

The preoperative parameter showed no significant difference in the systolic blood pressure, diastolic blood pressure and the pulse rate between the two groups.

Table 3 : Intra operative BP from SAB to delivery

Intra operative BP	INF group		CON group		'p'
	Mean	SD	Mean	SD	
At 1 min	122.1	9.7	121.4	7.9	0.5215 (NS)
At 2 min	117.5	13.1	114.8	12.7	0.2759 (NS)
At 3 min	121.8	16.0	106.5	11.8	0.0001(**S**)
At 4 min	124.2	10.7	105.1	9.8	0.0001 (**S**)
At 5 min	126	9.6	99.8	11.0	0.0001(**S**)
At 6 min	124.8	13	92	7.2	0.0001 (**S**)
At 7 min	125.6	10	102	9.9	0.0001 (**S**)
At 8 min	120.7	12.8	111.6	9.0	0.0008 (**S**)
At 9 min	120	11.1	120	-	0.8383 (NS)

S: significant

NS: not significant

In the infusion group systolic blood pressure was maintained to normal. There was statistically significant difference in the systolic blood pressure between the two groups, from 3rd minute till the delivery of the baby with a ‘p’ value of 0.0001

Table 4 : Intra operative PR from SAB to delivery

Intraoperative PR	INF group		CON group		‘p’
	Mean	SD	Mean	SD	
At 1 min	82.2	9	80.3	11.6	0.5101 (NS)
At 2 min	77.4	10	78.3	11.2	0.7347 (NS)
At 3 min	70.8	8.9	80.4	12.2	0.0001 (**S**)
At 4 min	65.4	7.6	69.9	11.2	0.1501 (NS)
At 5 min	67.0	12.5	69.5	12.3	0.9917 (NS)
At 6 min	68.8	15.3	69.6	10.6	0.7141 (NS)
At 7 min	73.7	8.4	72.3	8.9	0.4446 (NS)
At 8 min	75.7	7.6	65.1	7.4	0.0001 (**S**)
At 9 min	71.5	8.3	60	-	0.227 (NS)

S: significant

NS: not significant

Pulse rate changed according to the usage of the drug. There was statistical difference in the pulse rate at the 3rd and 8th minute with a ‘p’ value of 0.0001.

Table 5 : Time interval from SAB

Time (in minutes)	INF group		CON group		'p'
	Mean	SD	Mean	SD	
From SAB to Skin incision	4.22	0.42	4.8	0.4	0.0001 (S)
From skin to uterus	2.28	0.45	2.02	0.14	0.0003 (S)
From uterus to baby delivery	1.14	0.35	1.0	0	0.0063 (S)
Total time from SAB to Baby delivery	7.64	0.75	7.82	0.44	0.0501 (NS)

S: significant

NS: not significant

The time interval between the SAB to skin incision, skin to uterus incision, uterus incision to baby delivery time showed statistically significant difference. But the total time between the SAB to the baby delivery showed no significant difference. The average time was 7.6 min in the infusion group compared to 7.8 minutes in the control group.

Table 6: Total dose of Phenylephrine

Total dose of Phenylephrine in µg	INF group		CON group	
	NO	%	NO	%
Upto 200	-	-	37	74
201-400	33	66	13	26
401- 600	17	34	-	-
>600	-	-	-	-
Range Mean SD	300-600 402 91.5		100-300 212 62.2	
'p'	0.0001 significant			

The total dosage in the infusion group ranged between 300 to 600 µg. In the control group it ranged between 100 to 300µg. The difference between the 2 groups was statistically significant with a 'p' value of 0.0001.

Table 7: APGAR Score

APGAR Score	INF group		CON group	
	NO	%	NO	%
<u>1 minute</u>				
5	-	-	1	2
6	5	10	15	30
7	34	68	34	68
8	11	22	-	-
Range	5-8		5-7	
Mean	7.12		6.66	
SD	0.56		0.52	
‘p’	0.0001 significant			
<u>At 5 minutes</u>				
7	3	6	3	6
8	36	72	46	92
9	11	22	1	2
Range	7-9		7-9	
Mean	8.16		7.96	
SD	0.51		0.28	
‘p’	0.0001 - significant			

The APGAR score at the 1st and the 5th minute showed better in the infusion group and that was also statistically significant. It was 7.1 at 1st minute in the infusion group compared to 6.6 in the control group. It was 8.6 at 5th minute in the infusion group compared to 7.9 in the control group. APGAR scores were significant between the two groups in the 1st and 5th minute with a ‘p’ value of 0.0001.

Table 8: ABG pH values

pH values	Inf. Group			Con. Group			'p'
	Range	Mean	S.D.	Range	Mean	S.D.	
Umbilical artery pH	7.26-7.32	7.31	0.01	7.28-7.34	7.30	0.02	0.4337 (NS)
Umbilical vein pH	7.33-7.39	7.36	0.02	7.33-7.39	7.35	0.02	0.8771 (NS)

Table 9: PCO2 values

PCO2 values	Inf. Group			Con. Group			'p'
	Range	Mean	S.D.	Range	Range	S.D.	
Umbilical artery PCO2	48-58	51	2.7	49-56	53	2.2	0.0543 (NS)
Umbilical vein PCO2	40-48	44	1.9	40-48	44	1.9	0.7889 (NS)

S: significant

NS: not significant

The umbilical cord blood gas values showed no significant difference between both the groups, and they were comparable to the standard values.

Table 10: Atropine usage

Incidence of atropine usage	**INF group**		**CON group**	
	Total NO.	**%**	**Total NO.**	**%**
YES	**11**	**22**	**23**	**46**
NO	**39**	**78**	**27**	**54**
'P'	**0.0202 SIGNIFICANT**			

The usage of atropine was more in the control group which means that 22% of the patients had bradycardia in the infusion group which required treatment and 46% of patients in the control group required treatment with Atropine which was statistically significant with a 'p' value of 0.0202.

Table 11: Nausea /Vomiting

Incidence of Nausea /Vomiting	INF group		CON group	
	Total NO.	%	Total NO.	%
Yes	-	-	-	-
No	50	100	50	100
'p'	-			

There was not even a single case of nausea and vomiting in both the groups.

Table 12: Total episodes of Hypotension

Total episodes of hypotension	INF group		CON group	
	NO	%	NO	%
0	16	32	-	-
1	8	16	6	12
2	24	48	31	62
3	1	2	13	26
4	1	2	-	-
Range	0-4		1-4	
Mean	1.26		2.14	
SD	1.0		0.61	
‘p’	0.0001 significant			

In the infusion group 32% of the cases did not have a single episode of hypotension. In the control group all cases had hypotension. But both in the infusion and the control group there were maximum cases which had 2 episodes of hypotension. There was 48% of cases in the infusion group and 62% of cases in the control group. The mean episode of hypotension was 1.2 in the infusion group and 2.1 in the control group which was statistically significant with a ‘p’ value of 0.0001.

DISCUSSION

The commonly used techniques for cesarean section are general anaesthesia, epidural anaesthesia, and spinal anaesthesia. There are advantages as well as disadvantages in all these techniques. Whenever there is necessity for rapid induction like in fetal distress, antepartum hemorrhage or placenta previa general anaesthesia is indicated. Also in general anaesthesia, there will be less chances of hypotension, more cardiovascular stability and better control of airway and ventilation. But there are some disadvantages in general anaesthesia like maternal aspiration, sympathetic stimulation during laryngoscopy and intubation, awareness during anaesthesia and intubation difficulty in pregnancy. To over come these problems, spinal anaesthesia or epidural anaesthesia are the solutions. But in epidural anaesthesia there are many disadvantages like failure even in expert hands, delay in onset time, accidental total spinal anaesthesia, patchy analgesia and height of analgesia is not predictable. So spinal anaesthesia is now commonly used for cesarean sections especially in emergency cases.

There are many advantages and disadvantages of spinal anaesthesia over general anaesthesia.

ADVANTAGES:

1. Administered easily
2. High success rate
3. Produces rapid, reliable and profound anaesthesia
4. Fulfillment of mothers desire to stay awake
5. Avoidance of depressant drugs to the mother and subsequently to the fetus
6. Operative blood loss is less with regional anaesthesia

DISADVANTAGE:

1. Spinal anaesthesia induced hypotension will aggravate the supine hypotension syndrome of pregnancy.
2. Onset and time required for anaesthesia induction is less suitable when surgical indication is urgent.

Hypotension is associated with comparable fall in uterine blood flow and placental perfusion leading to fetal hypoxemia and acidosis if not promptly treated. Abnormal APGAR, fetal acidosis and neurobehavioural scores were noted when maternal systolic blood pressure dropped by more than 30% of baseline or stayed less than 80mm Hg for more than 4 minutes. Spinal anaesthesia also causes fetal heart rate distortions due to decline in the utero-placental blood flow. Spinal anaesthesia decreases the intervillous blood flow which is a measure of the changes in the uteroplacental blood flow in humans.

Prophylaxis against rather than treatment of this hypotension is important not only in the interests of fetal well being, but because even transient hypotension by inducing maternal nausea and vomiting can undermine her confidence in the procedure and thus convert enjoyable and satisfying experience into a harrowing one for all concerned.

This study confirmed the clinical impression that starting a prophylactic infusion of Phenylephrine immediately after the induction of spinal anesthesia for cesarean delivery would be effective at reducing the incidence, frequency, and severity of hypotension. It is noteworthy that in the infusion group, despite the administration of a large total dose of Phenylephrine, the fetal acid-base status and clinical condition of infants were excellent and similar to those in the control group. Although it was found that a prophylactic infusion of Phenylephrine was effective, and was not associated with a detrimental effect on fetal acid-base status, it did not eliminate hypotension completely. This is partly explained by the limitations of our standardized study protocol. The study was designed to be as simple as possible, with one criterion for starting and stopping the infusion and one set infusion rate. Of note, in the infusion group who had one or more episodes of hypotension, the hypotension occurred after the initial infusion was stopped. In these cases, although the infusion was restarted when SBP decreased to less than baseline again, because Phenylephrine has latency for effect, transient hypotension occurred. Large total doses of Phenylephrine in the infusion group were used and in this group SBP increased transiently to values more than baseline in some patients. This may cause concern about potential adverse effects on uteroplacental blood flow. However, uteroplacental flow or resistance was not directly assessed, the high values for umbilical artery and venous pH in the present study are indirect evidence that there was no significant adverse effect. However, it should be noted that it was studied only in healthy patients undergoing emergency cesarean deliveries. It may not be valid to extrapolate our findings to patients with nonreassuring fetal HR patterns or impaired uteroplacental blood flow, to preeclamptic patients, or to patients with a very prolonged induction-to-delivery time.

HEMODYNAMIC PROFILE:

It was found that maternal HR was statistically significantly slower in the control group compared to the infusion group contrary to the study done by the Ngan kee et al. This could be attributed to the rate of injection of the drug which was faster in the bolus group. However, because these cases were not associated with hypotension, the likely mechanism was a baroreceptor reflex. There were no associated adverse clinical sequelae. Atropine was used in 11 of the 50 cases in the infusion group compared to 23 of the 50 cases in the control group. All the cases required only one dosage of atropine of 0.3 mg.

The maternal systolic blood pressure was maintained till the delivery of the baby in the infusion group, but in the control group systolic blood pressure decreased and this decrease was statistically significant every minute till the delivery of the baby with a ‘p’ value of 0.0001. In one case in the infusion group there was an increase in the blood pressure as soon as the infusion was started to more than 20% of the base line in that case it was a failed subarachnoid block which needed a repeat spinal. This case was excluded from the study group. The blood pressure became normal in 5 minutes

The time interval between the SAB to skin incision, skin to uterus incision, uterus incision to baby delivery time showed statistically significant difference. But the total time between the SAB to the baby delivery showed no significant difference. The average time was 7.6 min in the infusion group compared to 7.8 minutes in the control group.

The total dosage in the infusion group ranged between 300 to 600 µg. In the control group it ranged between 100 to 300µg. The difference between the 2 groups was statistically significant with a ‘p’ value of 0.0001.

In the infusion group 32% of the cases did not have a single episode of hypotension. In the control group all cases had hypotension. But both in the infusion and the control group there was maximum cases which had 2 episodes of hypotension there was 48% of cases in the infusion group and 62% of cases in the control group. The mean episode of hypotension was 1.2 in the infusion group and 2.1 in the control group which was statistically significant with a ‘p’ value of 0.0001. Despite a more frequent incidence of hypotension in the control group, it was found that fetal acid-base status was not worse compared with that in the infusion group. This likely reflects the fact that when hypotension occurred, it was treated promptly with boluses of Phenylephrine. In this study hypotension was defined as a decrease in SBP by more than 20% less than baseline. However, the exact degree of hypotension that should be treated is undetermined.

FETAL PROFILE:

The APGAR score at the 1^{st} and the 5^{th} minute showed better in the infusion group and that was also statistically significant. It was 7.1 at 1^{st} minute in the infusion group compared to 6.6 at the same time in the control group .It was 8.6 at 5^{th} minute in the infusion group compared to 7.9 at the same time in control group. It was significant with a ‘p’ value of 0.0001.

The umbilical cord blood gas values showed no significant difference between both the groups. And they were comparable to the standard values. There was not a single patient who reported with nausea or vomiting. This may be attributed to the Inj.Metoclopramide 10mg given as a premedication. The level of block measured at 10 minutes was one segment higher in the infusion group compared with the control group. Although the clinical significance of a one-segment difference in block height is uncertain, because a higher block level might result in a greater degree of sympathetic block, this should have predisposed to a more frequent incidence of hypotension in the infusion group compared with the control group. But this did not happen because of the prophylactic Phenylephrine given in the infusion group.

SUMMARY

The aim of this study is to prospectively compare two methods of administration of Phenylephrine, Infusion vs Bolus dose in prevention and treatment of hypotension in cesarean section under spinal anaesthesia.100 patients, all primi gravidas undergoing emergency cesarean section under subarachnoid block were randomly divided into two groups. In the **infusion group**, Phenylephrine 100µg /min was infused for the initial 3 minutes after the subarachnoid block and were supplemented with 100µg infusion, whenever the systolic blood pressure was below the baseline value. In the **control group,** Phenylephrine 100µg bolus was given when the systolic blood pressure decreased below 20% of the baseline value. The following were noted and recorded.

1. Pulse rate and blood pressure every one minute until delivery of the baby and every five minutes thereafter.
2. The time interval between subarachnoid block to skin incision, skin incision to uterine incision, and uterine incision to delivery of baby.
3. APGAR scores at 1 minute and 5 minutes to assess neonatal outcome.
4. Total dose of the Phenylephrine used until the delivery of the baby in both groups.
5. Total episodes of the hypotension.
6. Incidence of nausea and vomiting.

The following results were obtained. Of the 2 groups compared

1. Age and preoperative baseline parameters were comparable in both groups.
2. Blood pressure: There was significant difference in the magnitude of hypotension between both the groups with less hypotension in the infusion group. In the infusion group systolic blood pressure was maintained to normal, there was statistically significant difference in the systolic blood pressure between the 3rd minute till the delivery of the baby.
3. Pulse rate changed according to the usage of the drug. There was statistical difference in the pulse rate at the 3rd and 8th minute. It was better in the infusion group.
4. The total dosage in the infusion group ranged between 300 to 600 µg. In the control group it ranged between 100 to 300µg. The difference between the 2 groups was statistically significant.
5. Fetal outcome measured by APGAR score was better in the infusion group and it was clinically significant. At the same time fetal acid base status showed no significant difference, it was excellent in both the groups.
6. The usage of atropine was more in the control group compared to the infusion group.

CONCLUSION

In conclusion, these data suggest that a prophylactic Phenylephrine infusion is an effective and simple method of reducing the incidence and magnitude of hypotension during spinal anesthesia for cesarean delivery with no adverse effect on neonatal outcome when compared to Phenylephrine bolus usage.

BIBLIOGRAPHY

1. Roberts SW, Leveno KJ, Sidawi JE, et al. Fetal acidemia associated with regional anesthesia for elective cesarean delivery. Obstet Gynecol 1995;85:79 –83.

2. Mueller MD, Bru¨ hwiler H, Schu¨ pfer GK, Lu¨ scher KP. Higher rate of fetal acidemia after regional anesthesia for elective cesarean delivery. Obstet Gynecol 1997;90:131–4.

3. Ngan Kee WD, Lau TK, Khaw KS, Lee BB. Comparison of metaraminol and ephedrine infusions for maintaining arterial pressure during spinal anesthesia for elective cesarean section. Anesthesiology 2001;95:307–13.

4. Ngan Kee WD, Khaw KS, Lee BB, et al. Metaraminol infusion for maintenance of arterial pressure during spinal anesthesia for cesarean delivery: the effect of a crystalloid bolus. Anesth Analg 2001;93:703–8.

ANESTH ANALG 2004;98:815–21

5. Ngan Kee WD, Khaw KS, Lee BB, et al. A randomized controlled study of colloid preload before spinal anaesthesia for Caesarean section. Br J Anaesth 2001;87:772–4.

6. Thorp JA, Rushing RS. Umbilical cord blood gas analysis. Obstet Gynecol Clin North Am 1999;26:695–709.

7. Rout CC, Rocke DA, Levin J, et al. A reevaluation of the role of crystalloid preload in the prevention of hypotension associated with spinal anesthesia for elective cesarean section. Anesthesiology 1993;79:262–9.

8. Rout CC, Akoojee SS, Rocke DA, Gouws E. Rapid administration of crystalloid preload does not decrease the incidence of hypotension after spinal anaesthesia for elective Caesarean section. Br J Anaesth 1992;68:394 –7.

9. Jackson R, Reid JA, Thorburn J. Volume preloading is not essential to prevent spinal-induced hypotension at Caesarean section. Br J Anaesth 1995;75:262–5.

10. Husaini SW, Russell IF. Volume preload: lack of effect in the prevention of spinal-induced hypotension at caesarean section. Int J Obstet Anesth 1998;7:76 –81.

11. Ngan Kee WD, Khaw KS, Lee BB, et al. A dose-response study of prophylactic intravenous ephedrine for the prevention of hypotension during spinal anesthesia for cesarean delivery. Anesth Analg 2000;90:1390 –5.

12. Mercier FJ, Riley ET, Frederickson WL, et al. Phenylephrine added to prophylactic ephedrine infusion during spinal anesthesia for elective cesarean section. Anesthesiology 2001;95: 668–74.

13. Lee A, Ngan Kee WD, Gin T. A quantitative systematic review of randomized controlled trials of ephedrine versus phenylephrine for the management of hypotension during spinal anesthesia for cesarean delivery. Anesth Analg 2002;94:920 –6.

14. Cooper DW, Carpenter M, Mowbray P, et al. Fetal and maternal effects of phenylephrine and ephedrine during spinal anesthesia for cesarean delivery. Anesthesiology 2002;97:1582–90. OBSTETRIC ANESTHESIA NGAN KEE ET AL. 821 PHENYLEPHRINE INFUSION FOR CESAREAN DELIVERY

15. Ralston DH, Shnider SM, deLorimier AA. Effects of equipotent ephedrine, metaraminol, mephentermine, and methoxamine on uterine blood flow in the pregnant ewe. Anesthesiology 1974; 40:354–70.

16. James FM III, Greiss FC Jr, Kemp RA. An evaluation of vasopressor therapy for maternal hypotension during spinal anesthesia.Anesthesiology 1970;33:25–34.

17. Schwinn DA, Reves JG. Time course and hemodynamic effects of alpha-1-adrenergic bolus administration in anesthetized patients with myocardial disease. Anesth Analg 1989;68:571–8.

18. Wollman SB, Marx GF. Acute hydration for prevention of hypotension of spinal anesthesia in parturients. Anesthesiology 1968;29:374–80.

19. Ueyama H, He YL, Tanigami H, et al. Effects of crystalloid and colloid preload on blood volume in the parturient undergoing spinal anesthesia for elective cesarean section. Anesthesiology 1999;91:1571–6.

20. Vercauteren MP, Coppejans HC, Sermeus L. Anaphylactoid reaction to hydroxyethylstarch during cesarean delivery in a patient with HELLP syndrome. Anesth Analg 2003;96:859 –61.

21. Morgan PJ, Halpern SH, Tarshis J. The effects of an increase of central blood volume before spinal anesthesia for cesarean delivery: a qualitative systematic review. Anesth Analg 2001;92: 997–1005.

22. Birnbach DJ, Datta S. Intravenous fluid preload in the prevention of spinal block-induced hypotension in parturients. Anesthesiology 1994;80:701, 703–4.

23. Alahuhta S, Ra¨sa¨nen J, Jouppila P, et al. Ephedrine and phenylephrine for avoiding maternal hypotension due to spinal anaesthesia for caesarean section: effects on uteroplacental and fetal haemodynamics. Int J Obstet Anesth 1992;1:129 –34.

24. Hall PA, Bennett A, Wilkes MP, Lewis M. Spinal anaesthesia for Caesarean section: comparison of infusions of phenylephrine and ephedrine. Br J Anaesth 1994;73:471–4.

25. .Robert K. Stoelting, Pharmacology and Physiology in Anaesthetic practice ,3rd Edition.

26.Ronald D Miller Anaesthesia 6th Edition.

27. Brooker, Robert F. MD; Butterworth, John F. IV MD; Treatment of Hypotension after Hyperbaric Tetracaine Spinal Anesthesia: A Randomized, Double-blind, Cross-over Comparison of Phenylephrine and EpinephrineAnesthesiology: April 1997 - Volume 86 - Issue 4 - pp 797-805 Clinical Investigation

28. Good man and Gillman's text book of pharmacology

29.Text book of pharmacology – K.D. Tripathy 6th edition

30. G. Edward Morgan, Jr. Maged S. Mikhail, Michael J. Murray ; Clinical Anesthesiology.

PROFORMA

NAME: AGE:
IPNO:
DIAGNOSIS: G/P/L/A:
PROCEDURE:
ASA: I / II
PREMEDICATION: Inj.Ranitidine 50 mg iv
Inj.Metoclopramide 10 mg iv
PRE OP BP : I : II: III: MEAN:
80%VALUE:

HR: I: II: III: MEAN:
No IV Prehydration
IV RL solution @5 ml/min
SAB LEVEL: L2-L3
GAUGE: 25G
VOLUME 1.8 ML OF 0.5% HYPERBARIC BUPIVACAINE
TIME OF SAB:

Patient turned supine
Left uterine displacement
No routine preoxygenation
GROUP: INFUSION/CONTROL

INFUSION: Phenylephrine 100µg/min for the initial 3 min, and 100µg whenever the systolic blood pressure goes below the baseline value

CONTROL: Phenylephrine 100µg whenever the systolic blood pressure goes below 20% of the baseline value

Upper sensory level of anaesthesia by loss of pinprick sensation: T2/T4/T6/T8
Treat bradycardia if HR <50 with Atropine 0.3 mg
Supplement oxygen if SPO2 < 95%

TIME	SYSTOLIC BP	HR	SPO2	PHENYLEPHRINE
1ST MIN				
2 MIN				
3 MIN				
4 MIN				
5 MIN				
6 MIN				
7 MIN				
8 MIN				
9 MIN				
10 MIN				

TIME OF SKIN INCISION:
TIME OF UTERINE INCISION:
TIME OF BABY DELIVERY:
TOTAL DOSE UNTIL THE BABY DELIVERY:
APGAR SCORE: 1 MIN: 5 MIN:
ABG ANALYSIS:
INCIDENCE OF NAUSEA/VOMITING YES/NO
TOTAL SURGERY DURATION:
SUPPLEMENTAL OXYGEN: YES/NO
TOTAL PHENYLEPHRINE USED:
TOTAL EPISODES OF HYPOTENSION:

STRUCTURE OF BUPIVACAINE

STRUCTURE OF PHENYLEPHRINE